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(54) Spherical granules having core and their production.

(57) The spherical granules having a core coated with spraying powder containing a drug and low substituted hydroxypropylcellulose, because of their excellent hardness, can be coated further evenly, (e.g. sustained release coating, gastric coating, enteric coating), and at the time the granules are excellent in disintegration.

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This invention relates to spherical granules having a core excellent in hardness and disintegration, and to their production.

Recently many studies have been made on drug delivery systems; especially as the dosage form for oral administration, granules coated with various coating agents, i.e. so-called coating granules have been used increasingly frequently, and the granules as they are or capsules produced by filling the granules in capsules have been developed.

As reasons for this fact may be mentioned that granules, as compared with tablets biopharmaceutically, reduce individual variations in gastric emptying rate, absorption, etc. and little affected by food (intake).

For production of spherical granules, the method wherein after granulation by extrusion the granules are made spherical with a marumerizer is most commonly used, but the granules thus produced are mostly not perfect spheres and the granule size distribution is wide; therefore it is said that uniform coating is so difficult that pharmaceutical preparations for precisely controlled release are difficult to be obtained.

On the other hand, recently a centrifugal fluidized-bed coating-granulator (sometimes abbreviated as CF granulator hereinafter) has been developed, and a method to make the granules spherical with this granulator has been tried.

In this method the surface of a spherical seed core or core is coated, while being sprayed with water or a solution containing a binder, with a spraying powder containing a drug, and thus spherical granules of high perfect sphere content and narrow granule size distribution are obtained. [See Drug Development and Industrial Pharmacy, 11(8), 1523-1541 (1985).]

To produce pharmaceutical preparations for controlled release the surface of the resulting spherical granules is coated with wax or polymer for the purpose of control of release of the drug. The coating is performed generally by fluidized-bed coating.

In the initial phase of the process of the fluidized-bed coating, there occur frequently troubles such as breaking and scraping of the spherical granules. These troubles not only damage the drug release control function but also affect greatly the yield in production of granules: thus a method for production of spherical granules excellent in hardness and disintegration has been desired

Under these circumstances, the inventors investigated the method for production of spherical granules excellent in hardness and disintegration by using the CF granulator, and have completed this invention.

This invention relates to

(1) spherical granules having a core coated with spraying powder containing a drug and low substituted hydroxypropylcellulose, and to

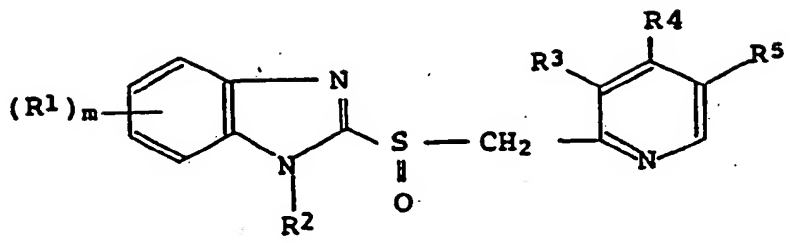
(2) a method for producing spherical granules having a core characterized in that seed cores are coated, while being sprayed with an aqueous binder, with spraying powder containing a drug and low substituted hydroxypropylcellulose.

The content of the hydroxypropoxyl group in the low substituted hydroxypropylcellulose (sometimes abbreviated as L-HPC hereinafter) used in this invention is generally about 4 - 20 %, preferably 5.0 - 16.0 %, more preferably 10.0 - 13.0 %. The mean particle size of the L-HPC may generally be not more than 200 μm in diameter, preferably not more than 100 μm, more preferably not more than 30μm.

The drugs are not particularly defined as far as they can be used in the form of granules, including drugs for the central nervous system such as diazepam, idebenone, aspirin, ibuprofen, paracetamol, naproxen, piroxicam, diclofenac, indometacin, sulindac, lorazepam, nitrazepam, phenytoin, acetoaminophen, ethenzamide, and ketoprofen; drugs for the circulatory system such as molsidomine, vinpocetine, propranolol, methyldopa, dipyridamole, furosemide, triamteren, nifedipine, atenolol, spironolactone, metoprolol, pindolol, captopril, and isosorbide nitrate; drugs for the respiratory system such as amlexanox, dextromethorphan, theophylline, pseudoephedrine, salbutamol, and guaifenesin; drugs for the digestive system such as benzimidazoles described below, cimetidine, ranitidine, pancreatin, and 5-aminosalicylic acid; antibiotics and chemotherapeutic agents such as cephalexin, cefaclor, cefradine, amoxicillin, pivampicillin, bacampicillin, dicloxacillin, erythromycin, erythromycin stearate, lincomycin, doxycycline, trimethoprim, and sulfamethoxazole; drugs for metabolic system such as serrapeptase, glibenclamide, and potassium chloride; and vitamin drugs such as vitamin B_1, vitamin B_2, vitamin B_6, vitamin C, and fursultiamine.

The said benzimidazoles include those described in US Patent No. 4045563, US Patent No. 4255431, European Patent Publication No. 45200 US Patent No. 4472409, European Patent Publication No. 5129, British Patent Publication No. 2134523, European Patent Publication No. 174726, European Patent Publication No. 175464, and European Patent Publication No. 208452 etc.

The benzimdazoles having antiulcer activity, which are described in the above laid-open patent specifications, for instance , are represented by the formula



wherein R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifuluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R^4 is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4.

The compounds of the formula (I) can be produced by the methods described in the above-cited laid-open patent specifications or modifications thereof.

In the following, brief mention is made of the substituents in those compounds which have the formula (I) and are already known.

Referring to R^1 in the above formula, C_{1-7} alkyls may be mentioned as the alkyl represented by R^1; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxy; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxyalkyl and C_{1-4} alkyls as the alkyl moiety; C_{1-4} alkyls as the alkyl moiety of the carbamoylalkyl: C_{1-5} alkoxys as the alkoxy; C_{1-7} alkyls as the alkyl moiety of the hydroxyalkyl; C_{1-4}alkanoyls as the acyl; phenyl as the aryl; phenyl as the aryl moiety of the aryloxy; C_{1-6} alkyls as the alkyl moiety of the alkylthio; and C_{1-6} alkyls as the alkyl moiety of the alkylsulfinyl.

Referring to R^2, C_{1-5} alkyls may be mentioned as the alkyl represented by R^2; C_{1-4} alkanoyls as the acyl; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxy; C_{1-4} alkyls as the alkyl moiety of the alkylcarbamoyl ; C_{1-4} alkyls as each of the alkyl moieties of the dialkylcarbamoyl: C_{1-4} alkyls as the alkyl moiety of the alkylcarbonylmethyl; C_{1-4} alkoxys as the alkoxy moiety of the alkoxycarbonylmethyl; and C_{1-4} alkyls as the alkyl moiety of the alkylsulfonyl.

Referring to R^3, R^4 and R^5, C_{1-4} alkyls may be mentioned as the alkyl represented by any of them; C_{1-8} alkoxys as the alkoxy; and C_{1-4} alkoxys as each of the alkoxy moieties of the alkoxyalkoxy.

Referring to R^4, C_{1-8} alkoxys may be mentioned as the alkoxy, which may optionally be fluorinated.

More specifically, they include 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole, and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole etc.

The said seed cores include Nonpareil produced by coating sucrose (75 weight parts) with corn starch (25 weight parts) according to the per se known method, and spherical seed cores using crystalline cellulose. The drug may be used as the seed core. The particle size of the said seed cores is generally 14-80 mesh.

The said aqueous binder includes water, ethanol (concentration: preferably 50% (v/v) or less), and solutions of binders in water or in ethanol; the concentration of the said solutions is generally 0.1 - 80% (w/v), preferably 0.5 - 70% (w/v). The said binders include sucrose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, pullulan, and gum arabic, which may be used alone or in combination.

The spraying powder containing the drug and L-HPC in this invention may be combined further with powdery additives. The said additives include excipients (e.g. lactose, corn starch, sucrose, crystalline cellulose, light anhydrous silicic acid), binders (e.g.α -starch, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, pullulan, dextrin, gum arabic), disintegrators (e.g. calcium carboxymethylcellulose, starch), stabilizers (e.g. magnesium carbonate, calcium carbonate, L-cystein), and coloring agents (e.g. talc, iron sesquioxide, tar colors).

The said spraying powder in this invention are obtained by mixing uniformly the drug, L-HPC, and the additives described above, and the particle size is generally not more than about 100 μm, preferably not more than about 50 μm.

The combination ratio of L-HPC to the spraying powder is preferably about 5 - 90% (w/w), more preferably about 10 - 60% (w/w).

The combination ratio of the drug to the spraying powder depends upon the kind and the dose of the drug,

being about 2 - 70% (w/w), preferably about 5 - 50% (w/w).

In the following the method for production of spherical granules having a core of this invention is descrived in detail. The conditions under which seed cores are coated with spraying powder while being sprayed with an aqueous binder are: the ratio of the aqueous binder to the spraying powder of about 1:1 - 1:2 is adequate; the production temperature need not be controlled, being generally room temperature (1 - 30°C). Spherical granules having a core of even size are obtained by sieving after drying. For example, 12 - 32 mesh round sieves are used, and the granules which pass through the 12 mesh sieve but do not pass through the 32 mesh sieve are selected.

The spherical granules having a core thus obtained may be coated according to the per se known method for the purpose of taste masking, enteric coating, gastric coating, or prolongation, and/or filled in capsules according to the per se known method.

The said coating agents include hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethyleneglycol, Tween 80, pluronic F 68, castor oil, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (Röhm Pharma Co., West Germany, acrylate copolymer), carboxymethylethylcellulose, polyvinylacetaldiethylaminoacetate, waxes, and pigments such as talc, titanium oxide, ferric oxide.

The spherical granules having a core of this invention, because of their excellent hardness, can be further coated evenly (e.g. sustained release coating, gastric coating, enteric coating), and at the same time the granules are excellent in disintegration.

In the following, this invention is illustrated in detail with working examples and experimental examples, which however should not limit this invention.

Example 1

Nonpareils (20 - 28 mesh), 2250 g, were brought into the CF granulator (CF-360, Freund Industrial Co., Ltd., Japan), and coated, while being sprayed with 2000 ml of hydroxypropylcellulose solution (3% (w/v)) at 25 ml/min, first with the spraying powder 1 and then the spraying powder 2, both of which had been prepared by mixing the ingredients listed below, at the rate of 45 g/min at room temperature with a rotor rotating at 200 rpm, dried under reduced pressure at 40°C for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12 - 32 mesh.

[spraying powder 1]

compound A*	450 g
magnesium carbonate	450 g
sucrose	450 g
corn starch	450 g
L-HPC	450 g

(degree of substitution with hydroxypropoxyl group: 10.0 - 13.0% (w/w), mean particle size: not more than 30 µm. The particles of the same degree of substitution and particle size were used hereinafter.)

* Compound A: 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)2-pyridyl]methylsulfinyl]benzimidazole

[spraying powder 2]

sucrose	420 g
corn starch	360 g
L-HPC	360 g

Example 2

The granules obtained in Example 1, 3800 g, were brought into the fluidized-bed coator (Okawara Co., Japan), subjected to enteric coating by spraying the enteric coating film solution described below at the rate of 50 ml/min under the controlled conditions of inlet air at 50°C and material temperature at 40°C, to give enteric coated spherical granules having core. The said granules were filled into No.2 hard capsules with a capsule filling machine (Parke-Davis Co., USA), to give capsules.

[Enteric coating film solution]

Eudragit L30D-55	628 g
talc	192 g
polyethyleneglycol 6000	64 g
titanium oxide	64 g
Tween 80	32 g
water	4400 ml

[composition of the capsules]

enteric coated granules	240 mg
No.2 hard capsule	65 mg
	305 mg (per capsule)

Example 3

Nonpareils (20 - 28 mesh), 85 g, were brought into a mini CF granulator(Freund Co.), and coated, while being sprayed with water (50 ml) at 2.5 ml/min, with the spraying powder described below at the rate of 5 g/min with a rotor rotating at 400 rpm, dried under reduced pressure at 40°C for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12 - 32 mesh.

[spraying powder]

pancreatin	20 g
sucrose	40 g
corn starch	20 g
L-HPC	20 g

Example 4

Nonpareils (24 - 32 mesh), 2 kg, were brought into a CF granulator (CF-360, Freund Co.), and coated, while being sprayed with 1% (w/v) hydroxypropylcellulose solution (1000 ml) at 20 ml/min, with the the spraying powder described below at the rate of 40 g/min with a rotor rotating at 200 rpm, dried under reduced pressure at 40°C for 16 hours, and sieved through round sieves, to give spherical granules having a oore of 12 - 32 mesh.

[spraying powder]

serrapeptase	50 g
sucrose	1350 g
corn starch	200 g
L-HPC	400 g

Then the granules thus obtained, 300 g, were brought into the fluidized-bed coator (Okawara Co., Japan), subjected to enteric coating by spraying the enteric coating film solution described below at the rate of 50 ml/min under the controlled conditions of inlet air at 50°C and material temperature at 40°C, to give enteric coated spherical granules having a core.

[Enteric coating film solution]

hydroxypropylmethylcellulose phthalate	1000 g
castor oil	100 g
talc	20 g
acetone	10000 ml

Example 5

Nonpareils (24 - 32 mesh), 85 g, were brought into a mini CF granulator (Freund Co.), and coated, while being sprayed with 50% (w/v) solution of sucrose (50 ml) at 5 ml/min, with the spraying powder described below at the rate of 10 g/min with a rotor rotating at 400 rpm, dried under reduced pressure at 40°C for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12 - 32 mesh.

[spraying powder]

molsidomine	5 g
sucrose	55 g
corn starch	20 g
L-HPC	20 g

Example 6

Nonpareils (24 - 32 mesh), 85 g, were brought into a mini CF granulator (Freund Co.), and coated, while being sprayed with 1% (-w/v) solution of hydroxypropylmethylcellulose (50 ml) at 2.5 ml/min, with the spraying powder described below at the rate of 5 g/min with a rotor rotating at 400 rpm, dried under reduced pressure at 40°C for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12 - 32 mesh.

[spraying powder]

idebenone	20 g
sucrose	20 g
corn starch	25 g
L-HPC	35 g

Example 7

Spherical seed cores of crystalline cellulose (20-32 mesh), 85 g, were brought into a mini CF granulator (Freund Co.), and coated, while being sprayed with 1% (w/v) solution of pullulan (50 ml) at 2.5 ml/min, with the the spraying powder described below at the rate of 5 g/min with a rotor rotating at 300 rpm, dried under reduced pressure at 40°C for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12 - 32 mesh.

[spraying powder]

amlexanox	25 g
hydroxypropylmethylcellulose	20 g
corn starch	25 g
L-HPC	30 g

Example 8

Crystals of vitamin C (42 - 60 mesh), 80 g, were brought into a mini CF granulator (Freund Co.), and coated, while being sprayed with 2% (w/v) solution of hydroxypropylcellulose (60 ml) at 2.5 ml/min, with the spraying powder described below at the rate of 5 g/min with a rotor rotating at 400 rpm, dried under reduced pressure at 40°C for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12-32 mesh.

[spraying powder]

cefaclor	50 g
sucrose	20 g
corn starch	10 g
L-HPC	40 g

Example 9

Crystals of sucrose (42-60 mesh), 85 g, were brought into a mini CF granulator (Freund Co.), and coated, while being sprayed with water (50 ml) at 2.5 ml/min, with the the spraying powder described below at the rate of 5 g/min with a rotor rotating at 400 rpm, dried under reduced pressure at 40°C for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12 - 32 mesh.

[spraying powder]

fursultiamine	5 g
sucrose	35 g
corn starch	30 g
L-HPC	30 g

Example 10

Nonpareils (20 - 28 mesh), 1650 g, were brought into the CF granulator (CF-360, Freund Co.), and coated, while being sprayed with 1050 ml of hydroxypropylcellulose solution (2% (w/v)) at 30 ml/min, first with the spraying powder 1 and then the spraying powder 2, both of which had been prepared by mixing the ingredients listed below, at the rate of 60 g/min at room temperature with a rotor rotating at 250 rpm, dried under reduced pressure at 40°C for 16 hours, and sieved through round sieves, to give spherical granules having a core of 14 - 32 mesh.

[spraying powder 1]

compound A*	450 g
magnesium carbonate	336 g
sucrose	297 g
corn starch	300 g
L-HPC	354 g

* Compound A: 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole

[spraying powder 2]

sucrose	300 g
corn starch	246 g
L-HPC	246 g

Example 11

The granules obtained in Example 10, 3800 g, were brought into the fluidized-bed coator (Okawara Co., Japan), subjected to enteric coating by spraying the enteric coating film solution described below at the rate of 50 ml/min under the controlled conditions of inlet air at 65°C and material temperature at 40°C, to give enteric coated spherical granules having core. To the said granules were added talc and light anhydrous silicic acid, then filled into No. 1 hard capsules with a capsule filling machine (Parke-Davis Co., USA) to give capsules.

[Enteric coating film solution]		
Eudragit L30D-55	2018 g	(solid: 605 g)
talc	182 g	
polyethyleneglycol 6000	60 g	
titanium oxide	60 g	
Tween 80	27 g	
water	4230 ml	
[composition of the capsules]		
enteric coated granules	348.8 mg	
compound A	30.0 mg	
magnesium carbonate	22.4 mg	
Nonpareils	110.0 mg	
sucrose	39.8 mg	
corn starch	36.4 mg	
L-HPC	40.0 mg	
hydroxypropylcellulose	1.4 mg	
Eudragit L 30D-55	44.6 mg	
talc	13.4 mg	
polyethyleneglycol 6000	4.4 mg	
titanium oxide	4.4 mg	
Tween 80	2.0 mg	
talc	0.6 mg	
light anhydrous silicic acid	0.6 mg	
No. 1 hard capsule	79.0 mg	
	429.0 mg	(per capsule)

Experimental Example 1

In the method of Example 3 , coating was performed with the spraying powder containing the ingredients listed in Table 1 in place of L-HPC to produce spherical granules having core. The said granules thus obtained (12 - 32 mesh), 5 g, were brought into a 50 ml stainless steel cylinder (50 ml, 32 mm in diameter), shaken in a mill (Spex Co., Spexmill) for 30 minutes, and sieved through a 32 mesh round sieve. The residual amount on the sieve was measured to calculate friability for evaluation of hardness of the granules. In addition, disintegration time was also determined according to the method described in the 11th Japanese Pharmacopoeia.

		Hardness(%)	Disintegration time
This invention	L-HPC	98	1 min
Controls	crystalline cellulose	87	2 min
	α-starch	89	not less than 30 min
	hydroxypropylcellulose	90	10 min
	hydroxypropylmethylcellulose	89	6 min
	polyvinylpyrrolidone	85	4 min
	pullulan	88	1.5 min
	methylcellulose	84	2 min
	dextrin	85	1 min
	gum arabic	82	1 min
	carboxymethylcellulose	86	2 min

These results show evidently that the spherical granules having a core of this invention are excellent in hardness and disintegration.

Claims

1. Spherical granules having a core coated with spraying powder containing a drug and low substituted hydroxypropylcellulose, characterised in that the drug is a drug for circulatory system, respiratory system, metabolic system, antibiotic, chemotherapeutic agent or vitamin.

2. Spherical granules according to claim 1, wherein the drug is diazepam, idebenone, aspirin, ibuprofen, paracetamol, naproxen, piroxicam, diclofenac, indometacin, sulindac, lorazepam, nitrazepam, phenytoin, acetoaminophen, ethenzamide, ketoprofen, molsidomine, vinpocetine, propranolol, methyldopa, dipyridamole, furosemide, triamteren, nifedipine, atenolol, spironolactone, metoprolol, pindolol, captopril or isosorbide nitrate, amlexanox, dextromethorphan, theophylline, pseudoephedrine, salbutamol, guaifenesin, cimetidine, ranitidine, pancreatin, 5-aminosalicylic acid, cephalexin, cefaclor, cefradine, amoxicillin, pivampicillin, bacampicillin, dicloxacillin, erythromycin, erythromycin stearate, lincomycin, doxycycline, trimethoprim or sulfamethoxazole, serrapeptase, glibenclamide or potassium chloride, vitamin B_1, vitamin B_2, vitamin B_6, vitamin C or fursultiamine.

3. Spherical granules according to claim 1, wherein the low substituted hydroxypropylcellulose has 4 to 20 % of the content of the hydroxypropoxyl group and is not more than 200 μm in diameter in mean particle size.

4. Spherical granules according to claim 1, wherein the spraying powder contains magnesium carbonate and/or calcium carbonate.

5. Spherical granules according to claim 1, wherein the spherical granules are further coated with spraying powder containing low substituted hydroxypropylcellulose.

6. Spherical granules according to claim 5, wherein the spherical granules are further coated with an enteric coating agent.

7. Spherical granules according to claim 6, wherein the enteric coating agent is acrylate copolymer or hydroxypropylmethylcellulose phtalate.

8. A method for producing spherical granules according to claim 1, characterised in that seed cores are

coated, while being sprayed simultaneously with an aqueous binder and with spraying powder containing the drug and low substituted hydroxypropylcellulose.

9. The method according to claim 8, wherein the seed cores are Nonpareils produced by coating 75 weight parts of sucrose with 25 weight parts of corn starch.

10. The method according to claim 8, wherein the spraying powder contains 5 to 90 % (w/w) of low substituted hydroxypropylcellulose.

11. The method according to claim 8, wherein the spraying powder contains 2 to 70 % (w/w) of the benzimidazole compound.

12. The method according to claim 8, wherein the ratio of the aqueous binder to the spraying powders is 1:1 to 1:2.

13. The method according to claim 8, wherein the spraying powder contains magnesium carbonate and/or calcium carbonate.

14. The method according to claim 8, wherein the spherical granules are further coated with spraying powder containing low substituted hydroxypropylcellulose.

15. The method according to claim 14, wherein the spherical granules are further coated with an enteric coating agent.

16. The method according to claim 15, wherein the enteric coating agent is acrylate copolymer or hydroxypropylmethylcellulose phtalate.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 20 2685

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	EP-A-0 200 902 (FUJISAWA PHARMACEUTICAL CO) * page 7; example 3 * * page 27; example 4 *	1-3	A61K9/50 A61K9/54
Y		4-7	
A		8-16	
P,Y	EP-A-0 210 540 (FUJISAWA PHARMACEUTICAL CO) * column 15 - column 16; examples 1-3 * &dk-a-8603445 (pub.20-01-1987)	5-7	
Y	EP-A-0 184 754 (HOECHST AG) * page 1, line 16 - line 25 * * page 3, line 34 - page 5, line 3 * * page 6, line 19 - page 7, line 11 * * page 10 - page 11; example 1 *	4	
P,X	EP-A-0 244 380 (AKTIEBOLAGET HASSLE) * page 13, line 6 - page 17, line 22 * * page 19 - page 21; examples 2,3 *	1-16	
P,A	EP-A-0 237 200 (TAKEDA CHEMICAL INDUSTRIES, LTD) * page 14 - page 15; examples 8,9 *	1-16	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	21 NOVEMBER 1991	BENZ K.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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